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REVIEW

Continuous renal replacement therapy and neurological dysfunction in septic acute kidney injury

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Abstract

Sepsis-associated acute kidney injury (SA-AKI) is a frequent and severe complication of critical illness and is increasingly recognized as a contributor to remote organ dysfunction, including the brain. Experimental and clinical data suggest that SA-AKI may exacerbate neurological injury through systemic inflammation, blood–brain barrier disruption, impaired cerebral autoregulation, and altered osmotic and metabolic homeostasis, providing a biological basis for a kidney–brain axis in sepsis. Continuous renal replacement therapy (CRRT) is the preferred renal replacement modality in patients with, or at risk of, hemodynamic instability and is central to the management of severe SA-AKI. Beyond its established role in solute and fluid control, CRRT may influence kidney and brain pathophysiology by modulating the inflammatory burden, acid–base balance, and hemodynamics; however, evidence for organ-protective effects remains inconsistent, and optimal prescription strategies remain undefined. This review synthesizes clinical and preclinical evidence examining the impact of CRRT on renal and neurological outcomes in SA-AKI, with a specific focus on treatment timing, intensity, and fluid management. We integrate mechanistic insights to highlight potential pathways linking CRRT prescription to kidney and brain injury, identify critical gaps in current knowledge, particularly regarding neurological and renal outcomes, and propose priorities for future research aimed at optimizing CRRT strategies in sepsis-associated multi-organ dysfunction.

Keywords

Continuous renal replacement therapy; Brain injury; Acute kidney injury; Septic acute kidney injury; Sepsis; Cognitive function

1. Introduction

Sepsis is a life-threatening condition caused by a dysregulated host response to infection, leading to multi-organ dysfunction. The kidney is particularly vulnerable, with sepsis being the leading cause of acute kidney injury (AKI) in intensive care units, accounting for approximately half of cases [1–3]. Sepsis-associated AKI (SA-AKI) develops in 50–70% of patients with septic shock, and 20–40% require renal replacement therapy [4]. SA-AKI is associated with high mortality, prolonged intensive care unit (ICU) stays, and progression to chronic kidney disease.

The pathophysiology of SA-AKI is complex and multifactorial, involving microcirculatory impairment, systemic inflammation, endothelial and glycocalyx dysfunction, mitochondrial derangements, and oxidative stress [5]. Importantly, SA-AKI can contribute to remote organ injury, including the brain, through systemic inflammation, accumulation of uremic toxins, blood–brain barrier (BBB) disruption, and impaired cerebral autoregulation, forming a biological basis for a kidney–brain axis in sepsis [6–9].

Continuous renal replacement therapy (CRRT) is the preferred modality for renal support in hemodynamically unstable patients with severe SA-AKI, providing solute clearance, fluid management, and acid–base regulation [10, 11]. Beyond these traditional roles, CRRT may influence kidney and brain pathophysiology by modulating inflammatory mediators, hemodynamic, and osmotic balance, although direct evidence linking CRRT prescription to neurological outcomes in sepsis is limited. Insights from related extracorporeal support modalities, such as cardiopulmonary bypass and extracorporeal membrane oxygenation, suggest potential organ-protective mechanisms, highlighting the need for future targeted investigations.

This review synthesizes clinical and preclinical evidence to advance a kidney–brain–CRRT framework in SA-AKI, positioning CRRT prescription parameters, including timing, intensity, and fluid management, as potentially modifiable determinants of both renal recovery and neurological outcomes. By integrating mechanistic insights with clinical data, this framework identifies critical knowledge gaps and informs fu-

ture research aimed at optimizing CRRT strategies to improve multi-organ outcomes in sepsis.

2. Pathophysiology of sepsis-associated acute kidney injury

Hemodynamic mechanisms resulting in renal hypoperfusion have previously been considered a leading cause of SA-AKI. It has been proposed that systemic vasodilation, reduced cardiac output states, and venous congestion can lower renal perfusion pressure and glomerular filtration, leading to global renal ischemia, cellular injury, and acute tubular necrosis [12]. However, preclinical and clinical reports have demonstrated that the first 48 hours of sepsis are often characterized by a hyperdynamic circulation, with increased cardiac output [13]. In support of this, several studies have shown that total renal blood flow may be preserved or even elevated in sepsis [13]. This finding suggests that impaired renal autoregulation and microcirculatory dysfunction, rather than global renal ischemia, may contribute to AKI. In sepsis, an uncoupling of the renal microcirculation from the macrocirculation has been demonstrated [14].

In ovine sepsis, selective renal medullary tissue ischemia and hypoxia occur up to 24 hours before the development of AKI, as characterized by elevated plasma creatinine, decreased creatinine clearance, and oliguria, despite increases in renal blood flow and preserved renal cortical perfusion and oxygenation [14]. Tissue perfusion and oxygenation of the renal cortex and medulla are not significantly different under healthy non-anesthetized conditions; however, the renal medulla appears to be more susceptible to ischemia and hypoxia under pathophysiological conditions, such as sepsis [14] and cardiopulmonary bypass [15]. Renal medullary tissue hypoxia occurs early and may trigger a downward spiral of oxidative stress, inflammation, mitochondrial dysfunction, and tubular injury that culminates in AKI [5]. Renal tissue hypoxia has emerged as an important pathophysiological mechanism underlying SA-AKI and the subsequent transition to chronic kidney disease (CKD) [4]. Furthermore, preclinical and clinical evidence suggests that SA-AKI is a functional rather than a structural defect [16, 17]. This concept has been demonstrated by the lack of acute tubular necrosis or extensive tubular apoptosis in patients who succumb to SA-AKI [18]. Similarly, histopathological and electron microscopy studies in clinically relevant sheep models of hyperdynamic SA-AKI have reported a lack of structural injury to the kidneys [16, 17].

Non-hemodynamic mechanisms are also recognized as important contributing causes of SA-AKI. Circulating cytokines such as tumor necrosis factor-α and interleukin-1β, together with reactive oxygen and nitrogen species, promote oxidative stress and tubular injury [19]. Endothelial and glycocalyx injury further compromises the renal microcirculation, leading to capillary leakage, tissue hypoxia, and amplification of local inflammation [12]. In contrast, recent molecular studies in sheep with SA-AKI have reported no evidence of oxidative or nitrosative stress in renal cortical or medullary tissue, due to overexpression of antioxidant defense pathways within the kidneys [20]. Sepsis-induced renal medullary hypoperfusion and hypoxia have been attributed to inflammation (overexpression of tumor necrosis factor-α) in the renal cortex and reduced nitric oxide bioavailability (Thr-495 phosphorylation of endothelial nitric oxide synthase) in the renal medulla [20]. Renal medullary tissue hypoxia, particularly in metabolically active regions of the kidneys, including the thick ascending limb of the Loop of Henle, can lead to mitochondrial dysfunction. This can impair adenosine triphosphate generation and perpetuate a cycle of metabolic dysfunction [21]. Collectively, these findings suggest that the notion of sepsis-induced oxidative stress in renal tissue reported in experimental sepsis may be species-, model-, or time-dependent [20]. Accordingly, a better understanding of the pathophysiology of SA-AKI may facilitate the development of effective mechanism-guided interventional strategies.

3. Continuous renal replacement therapy

Antibiotics, fluid resuscitation, and vasopressors are currently the mainstay treatments for patients with sepsis. Renal replacement therapy is recommended for patients with severe SA-AKI [19]. CRRT is used in many ICUs for patients with hemodynamic instability [11]. Because CRRT encompasses blood purification techniques intended to run for 24 hours or longer, unlike intermittent hemodialysis, CRRT is employed on an ongoing basis to achieve continuous solute and fluid homeostasis through convection, diffusion, or ultrafiltration. Therefore, CRRT may be hemodynamically better tolerated than intermittent hemodialysis due to its slower fluid removal and more gradual control of solute concentration [10, 11].

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines provide two non-graded recommendations regarding the timing of renal replacement therapy initiation. First, renal replacement therapy should be initiated urgently in the presence of life-threatening changes in fluid, electrolyte, or acid–base balance. Second, the decision to initiate renal replacement therapy should be based on the broader clinical context, the presence of conditions that can be managed with renal replacement therapy, and trends in laboratory tests rather than on single blood urea nitrogen and creatinine thresholds [10]. Furthermore, as described in the guideline as a potential application, CRRT may also be prescribed for non-emergent indications or for renal support [10]. Due to the lack of large-scale clinical studies, the criteria for cessation of CRRT in AKI remain uncertain [10]. Observational studies and meta-analysis have suggested that urine volume, creatinine clearance, and serum creatinine levels may be predictors of successful CRRT weaning protocols [22, 23].

On the other hand, to determine the optimal timing of initiation, treatment intensity, and fluid removal strategies of CRRT, several randomized controlled trials (RCTs) and observational studies have been conducted. However, their effects on clinical outcomes, including mortality, renal recovery, and neurological outcomes, have remained inconsistent and will be described in subsequent sections.

4. Impact of CRRT on the brain and kidneys

4.1 Effects of CRRT on the brain

Direct evidence examining the effects of CRRT on brain pathophysiology and neurological outcomes in septic AKI is limited. However, converging experimental and clinical data support a biologically coherent kidney-brain axis that is plausibly modulated by CRRT. Insights from related extracorporeal support settings, including cardiopulmonary bypass and extracorporeal membrane oxygenation, are incorporated where mechanistically informative, not to imply equivalence, but to contextualize shared pathways of BBB injury, neuroinflammation, and cerebral hypoperfusion. This framework positions CRRT as a potentially modifiable intervention along the kidney-brain axis, underscoring the need for dedicated experimental and clinical investigations to define how CRRT prescription parameters, including timing, intensity, and fluid management, modulate neurological and cognitive outcomes alongside renal outcomes in sepsis.

The establishment of a proinflammatory milieu in SA-AKI and AKI is associated with modulation of other kidney-brain axis pathways [8]. The upregulation of tumor necrosis factor-α and interleukin-6 in the injured kidney, along with increases in uremic molecules, is thought to mediate the effects of AKI on other vital organs [8, 9]. Animal studies have demonstrated that inflammation in the brain can occur following AKI, and this inflammation is accompanied by increased vascular permeability in the brain [9]. These findings indicate a disruption of the BBB [9]. Furthermore, kidney injury may enhance the release of cytokines and chemokines, allowing them to infiltrate the brain through the disrupted BBB, leading to brain injury [24]. These infiltrating cytokines can cause microglial activation and further BBB disruption in patients with AKI. In addition, oxidative stress and dysregulation of water balance, involving aquaporins, can contribute to cytotoxic brain oedema [24]. Encephalopathy is a well-known uremic symptom and is partly associated with blood urea nitrogen levels. In critically ill patients, even low levels of uremic toxins can cause cognitive impairment more rapidly and severely than in patients with CKD [25]. Additionally, the altered metabolism of centrally acting drugs may affect neurological outcomes, and this must be taken into consideration.

CRRT controls volume overload and uremic toxins, which may provide theoretical advantages in mitigating injury of vital organs caused by AKI. However, further studies are needed to establish the interaction between CRRT and the crosstalk between vital organs. Preclinical and clinical studies have suggested that CRRT can attenuate systemic inflammation [26] and avoid rapid osmotic shifts compared with intermittent hemodialysis. Together with evidence that AKI can disrupt the BBB, these findings support the possibility that CRRT could provide benefits by limiting cerebral edema and preserving BBB integrity (Fig. 1).

However, bioincompatibility-related risks of CRRT warrant consideration. Synthetic membrane–blood interactions may contribute to augmented peripheral- and neuro-inflammation [27]. Elsaafien *et al*. [28] demonstrated that exposure to the circuit and tubing in cardiopulmonary bypass caused exaggerated peripheral inflammation, leading to pronounced neuroinflammation across the frontal, temporal and parietal cortical regions in the brain. Prolonged exposure of blood to extracorporeal membranes and plastic tubing can activate the complement and coagulation pathways, as well as leukocytes, amplifying systemic inflammation and endothelial dysfunction, which has also been described in cardiopulmonary bypass and extracorporeal membrane oxygenation [29]. Future studies should explore whether a similar pathological phenomenon occurs during the implementation of CRRT in SA-AKI.

In terms of hemodynamics, CRRT has theoretical advantages, such as slower fluid removal, which improves hemodynamic stability and fluid balance, and gradual solute control, which avoids large fluctuations and fluid shifts [10]. This may thereby reduce complications, such as hypotension and dialysis disequilibrium syndrome. Despite these theoretical advantages, clinical trials have not demonstrated improved survival with CRRT compared with intermittent hemodialysis in patients with AKI [11]. In patients with CKD, two prospective studies have shown decreased intradialytic cerebral perfusion [30, 31], which is related to dialysis-related factors such as intradialytic hypotension or ultrafiltration volume. Findlay *et al*. [32] demonstrated that cerebral blood flow declined significantly during dialysis, correlating with the volume of ultrafiltrate. The percentage of decline in cerebral blood flow was associated with an intradialytic decline in cognitive function. A decrease in cerebral blood flow and cerebral perfusion has been consistently observed in septic shock [33], and impairment of cerebral autoregulation is associated with delirium [34]. Therefore, inadequate prescription of CRRT may further contribute to cerebral hypoperfusion and aggravate neurological dysfunction in patients with sepsis-associated encephalopathy.

4.2 Effects of CRRT on the kidneys

CRRT is used to support kidney function during AKI by controlling solute, electrolyte, and fluid balance. Beyond these supportive effects, several studies suggest that CRRT may attenuate renal inflammation by removing circulating cytokines, pathogen-associated molecular patterns, and damage-associated molecular patterns, thereby reducing oxidative stress, endothelial injury, and tubular apoptosis [26]. In patients with sepsis, the levels of inflammatory and anti-inflammatory mediators are positively correlated with mortality; therefore, the removal or adsorption of these mediators may improve patient outcomes [26]. Based on this concept, different extracorporeal blood purification therapies have been developed to remove excess cytokines and endotoxins. However, clinical evidence remains inconclusive and has not consistently demonstrated improvements in mortality, renal recovery, or neurological outcomes [35].

As with the brain, bioincompatibility-related risks of CRRT also warrant consideration for the kidneys. Membrane biocompatibility is essential for safe and effective CRRT, while bioincompatibility can trigger complement activation, inflammation, and coagulation disorders in addition to reducing efficacy [36]. These responses to membrane-blood interactions may

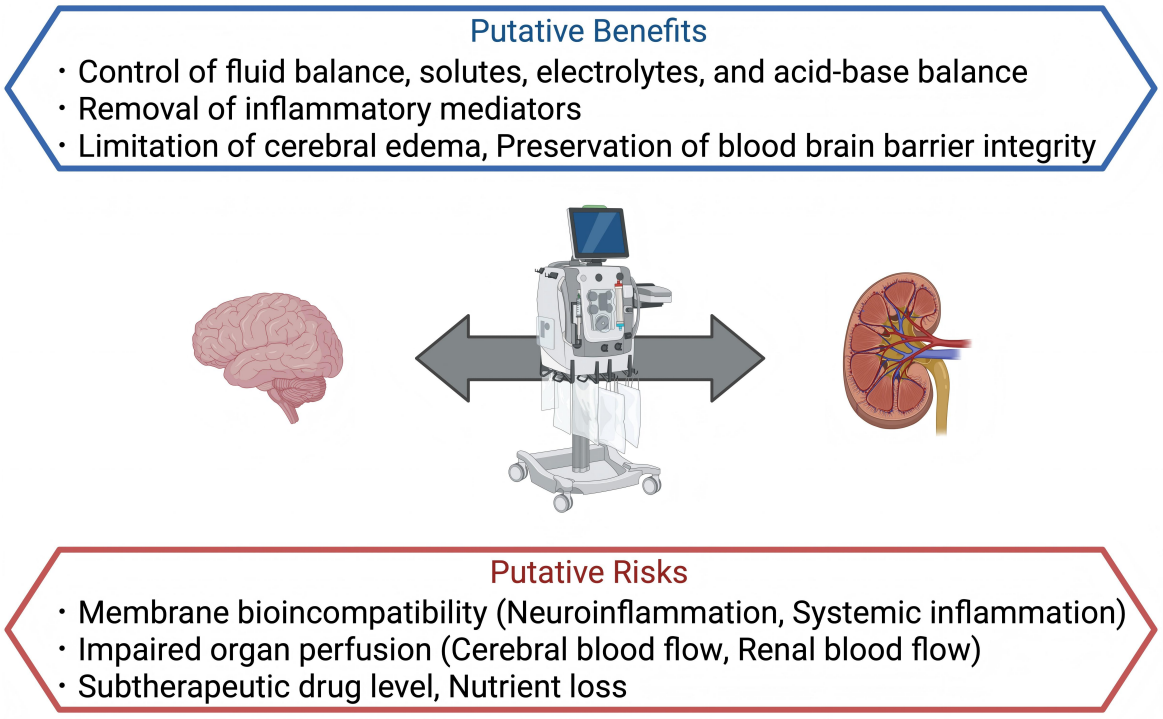

FIGURE 1. Potential benefits and risks of continuous renal replacement therapy in sepsis-associated acute kidney injury on the kidneys and brain.

induce oxidative stress, endothelial dysfunction, and immune activation, thereby affecting patient outcomes [27].

Excessive ultrafiltration leading to a negative fluid balance may exacerbate hypotension and renal ischemia, while a positive fluid balance is associated with higher mortality [37–40]. Several studies have suggested that hemodynamic instability related to CRRT is associated with increased mortality and may impair kidney recovery [41, 42]. In a study of intermittent hemodialysis, an acute decrease in renal perfusion was observed, even in the absence of pronounced hypotension [43]. Thus, renal tubular injury due to repetitive, intradialytic ischemic AKI may contribute to kidney injury, resulting in poor long-term outcomes. On the other hand, a preclinical study demonstrated that, although blood pressure, cardiac index, and urine output significantly decreased after the initiation of CRRT, renal blood flow steadily increased throughout the study [44]. Further preclinical and clinical studies are needed to elucidate the exact mechanisms underlying hemodynamics changes and kidney injury during CRRT.

There are also concerns regarding nutrition and drug delivery as part of CRRT. Both factors are essential components in the management of critically ill patients, including those with sepsis. However, CRRT may clear antibiotics and nutrients excessively, leading to subtherapeutic drug levels or malnutrition [45, 46]. Furukawa *et al.* [47] reported the sorbent-based removal ratio of antibiotics. Existing data suggest that drug removal varies depending on the specific drug and the cartridge, so that dose adjustment may be required to achieve appropriate therapeutic levels [48]. Furthermore, the variability in sorbent-based clearance between different drugs highlights the importance of individually assessing drug-sorbent interactions for all key antimicrobials [47]. In critically ill patients receiving CRRT, switching to extended or continuous infusions and performing therapeutic drug monitoring may be a practical approach to ensure the achievement of antibiotic therapeutic targets [49].

5. Prescription of CRRT in SA-AKI

Emerging evidence suggests that key CRRT prescription parameters may influence both renal and neurological outcomes in septic AKI. The timing of CRRT initiation may affect the duration of exposure to uremic toxins, inflammatory mediators, and metabolic derangements that contribute to renal non-recovery and cerebral dysfunction, while CRRT intensity and solute clearance may modulate neurotoxic burden and acid–base homeostasis. In parallel, fluid management during CRRT directly impacts cerebral perfusion and intracranial pressure through its effects on systemic hemodynamics, venous congestion, and osmotic gradients, providing a plausible mechanistic link between CRRT prescription and kidney–brain outcomes. Several RCTs have investigated the prescription of CRRT for AKI. However, gaps remain in the current evidence regarding the effects of these interventions on renal and neurological outcomes. The following section summarizes several clinical interventions that have been evaluated to date and the patient outcomes reported.

5.1 Timing of initiation

The optimal timing of CRRT initiation in SA-AKI remains controversial (Table 1, Ref. [22, 50–53]). Traditional life-threatening indications include refractory hyperkalemia, severe metabolic acidosis, overt uremia, and fluid overload [10]. The single-center Early *vs.* Late Initiation of Renal Replace-

TABLE 1. Clinical studies evaluating timing of initiation.

Authors (Year)	Study Design Intervention *vs.* Control	Main Findings
Zarbock A *et al.* [22] (2016) ELAIN trial	RCT Single-center (ICU in Germany) Patients: mostly post-surgery with AKI Early (n = 112) *vs.* Delayed (n = 119) Early: ≤8 h of KDIGO stage 2 AKI Delayed: ≤12 h of KDIGO stage 3 AKI or absolute indications Primary outcome: 90-day mortality	Early RRT initiation was associated with a significantly lower 90-day mortality (Early 39.3% *vs.* Delayed 54.7%). Duration of RRT and length of hospital stay were significantly shorter with early initiation. No significant difference was observed in RRT requirement after day 90, organ dysfunction, or length of ICU stay.
Gaudry S *et al.* [50] (2016) AKIKI trial	RCT Multicenter (31 ICUs in France) Patients: critically ill patients receiving invasive mechanical ventilation, catecholamine infusion, or both with KDIGO stage 3 AKI (SA-AKI: 80%) Early (n = 311) *vs.* Delayed (n = 308) Early: ≤6 h of KDIGO stage 3 Delayed: only if absolute indications, oliguria or anuria lasting for more than 72 h Primary outcome: 60-day mortality	No significant difference was observed in 60-day mortality (Early 48.5% *vs.* Delayed 49.7%). Nearly half of the patients in the delayed-strategy group did not receive RRT.
Barbar SD *et al.* [52] (2018) IDEAL-ICU trial	RCT Multicenter (29 ICUs in France) Patients: patients with septic shock and AKI at the failure stage of the RIFLE classification Early (n = 246) *vs.* Delayed (n = 242) Early: ≤12 h after the onset of AKI Delayed: ≥48 h if no emergency indication Primary outcome: 90-day mortality	The trial was stopped early for futility, with no difference in 90-day mortality (Early 58% *vs.* Delayed 54%). In the delayed-strategy group, 38% of patients did not receive RRT.
Bagshaw SM *et al.* [51] (2020) STARRT-AKI trial	RCT Multicenter (168 ICUs in 15 countries) Patients: critically ill patients with KDIGO stage 2 or 3 AKI (SA-AKI: 57.7%) Accelerated (n = 1468) *vs.* Standard (n = 1460) Accelerated: ≤12 h of eligibility criteria Standard: only if conventional indications or ≥72 h Primary outcome: 90-day mortality	No reduction was observed in 90-day mortality (Accelerated 43.9% *vs.* Standard 43.7%). Continued dependence on RRT at 90 days was higher in the accelerated-strategy group (Accelerated 10.4% *vs.* Standard 6.0%).
Gaudry S *et al.* [53] (2021) AKIKI-2 trial	RCT Multicenter (39 ICUs in France) Patients: critically ill patients receiving invasive mechanical ventilation, catecholamine infusion, or both with KDIGO stage 3 AKI (SA-AKI: 54%) Delayed (n = 137) *vs.* More-delayed (n = 141) Delayed: ≥72 h oliguria or BUN ≥112 mg/dL More delayed: ≥72 h, but wait until BUN ≥140 mg/dL or urgent indication Primary outcome: RRT-free days between randomization and day 28	No difference was observed in RRT-free days (Delayed 12 days *vs.* More delayed 10 days). No significant difference was observed in 60-day mortality (44% *vs.* 55%). Longer postponement of RRT initiation provided no additional benefit and was associated with potential harm.

RCT: Randomized Controlled Trial; ICU: Intensive Care Unit; AKI: Acute Kidney Injury; KDIGO: Kidney Disease: Improving Global Outcome; RRT: Renal Replacement Therapy; SA-AKI: Sepsis-Associated Acute Kidney Injury; ELAIN: Early vs. Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury; AKIKI: Artificial Kidney Initiation in Kidney Injury; IDEAL-ICU: Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit; STARRT-AKI: Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury; RIFLE: Risk, Injury, Failure, Loss, End-stage kidney disease; BUN: blood urea nitrogen.

ment Therapy in Critically Ill Patients with Acute Kidney Injury (ELAIN) trial [22] suggested that early initiation improved 90-day survival and renal recovery. However, larger multicenter trials have shown different results. The Artificial Kidney Initiation in Kidney Injury (AKIKI) trial [50] and the Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial [51] both found no mortality benefit with early initiation compared with a delayed strategy, highlighting the risks of unnecessary renal replacement therapy exposure. The Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial [52], conducted in patients with septic shock, was stopped early due to futility and even suggested potential harm with early initiation. The Artificial Kidney Initiation in Kidney Injury 2 (AKIKI-2) trial [53] examined a more delayed strategy and reported a possible increase in 60-day mortality, indicating that excessive delay may also be associated with potential harm.

However, the characteristics of patients, especially those with SA-AKI, varied among the studies. In the STARRT-AKI trial, there was no evidence of substantial between-group heterogeneity in treatment effects regarding 90-day mortality across subgroups, including patients with sepsis [51]. In a multivariable analysis of the AKIKI-2 trial, risk factors associated with 60-day mortality included a more delayed strategy, the Simplified Acute Physiology Score III, and mechanical ventilation, whereas sepsis was not a significant factor [53].

These RCTs mainly focused on short-term mortality and renal recovery. Although short-term organ dysfunction, such as the Sequential Organ Failure Assessment (SOFA) score, was assessed in some studies, more detailed neurological outcomes were not evaluated.

5.2 Treatment intensity

CRRT intensity has been extensively studied (Table 2, Ref. [54–57]). In 2000, Ronco *et al*. [58] observed that survival at 15 days was significantly higher in the 35 or 45 mL/kg/h groups compared with the 20 mL/kg/h group. However, large RCTs have consistently reported negative findings. The Veterans Administration/National Institutes of Health (VA/NIH) Acute Renal Failure Trial Network (ATN) Study [54] compared intensive therapy with standard therapy, finding no difference in survival or renal recovery. The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy study [55] compared 40 *vs*. 25 mL/kg/h, and the hIgh VOlume in Intensive caRE (IVOIRE) trial [56] compared 70 *vs*. 35 mL/kg/h; both confirmed the absence of benefit from higher-intensity regimens. In the RENAL study, mortality was similar between the two treatment groups in all prespecified subgroups, including patients with sepsis. In these RCTs, neurological outcomes were not evaluated. Based on these results, the KDIGO guidelines recommend a delivered effluent dose of 20–25 mL/kg/h [10]. Increasing dose solely for cytokine clearance has not translated into clinical benefit and may increase the risk of nutrient loss and subtherapeutic drug levels [56].

In contrast, observational data from Japan have suggested that even lower-intensity regimens may be sufficient to maintain acid–base homeostasis without compromising short-term outcomes [57, 59]. Building on these findings, the ongoing Low-Intensity versus Medium-Intensity Continuous Kidney Replacement Therapy (LIMIT) trial (NCT06014801) is directly testing whether a lower prescription (12 mL/kg/h) is superior to the guideline-recommended 25 mL/kg/h in critically ill patients with AKI. Similar trials are ongoing in Germany (KETZEREI trial, NCT06021288) and in Canada (WISDOM trial, NCT06446739) as pilot feasibility trials.

5.3 Fluid management

Managing fluid balance is crucial in CRRT (Table 3, Ref. [37–40]). In patients with SA-AKI, a positive cumulative fluid balance is strongly associated with mortality through mechanisms such as tissue edema, impaired oxygen delivery, and organ congestion. This relationship has been consistently observed in large observational cohorts such as the Sepsis Occurrence in Acutely ill Patients (SOAP) study [37] and the Finnish Acute Kidney Injury (FINNAKI) study [38], as well as in *post-hoc* analyses of RCTs: in the RENAL trial, patients with greater fluid accumulation had significantly worse outcomes [39, 40]. Conversely, overly aggressive fluid removal can cause hypotension, impair renal recovery, and compromise cerebral perfusion, potentially worsening sepsis-associated encephalopathy or long-term cognitive outcomes [40]. Analyses of net ultrafiltration rates reveal a U-shaped relationship, with excessive rates ($>$1.75 mL/kg/h) associated with increased mortality [40] (Table 3).

Unlike the timing of initiation or treatment intensity, there are no large RCTs specifically addressing fluid management strategies in SA-AKI. Studies are needed to establish optimal ultrafiltration strategies that can minimize fluid overload without compromising systemic or cerebral perfusion. The NEPTUNE study, an RCT comparing net ultrafiltration rates, is currently underway (NCT02542293). In the NEPTUNE study, investigators aim to compare the hemodynamic effects of targeted net ultrafiltration rates ($<$1.75 mL/kg/h) during CRRT. The research hypothesis is that limiting net ultrafiltration rate minimizes hemodynamic instability related to renal replacement therapy and may therefore enhance renal recovery.

At this time, individualized ultrafiltration based on each patient's hemodynamic status is recommended based on clinical assessment and hemodynamic monitoring, rather than fixed targets, recognizing the dynamic and heterogeneous nature of septic shock.

5.4 Limitations and future directions

As discussed above, current evidence suggests that routine early initiation of CRRT does not provide a clear benefit, whereas excessive delay may be harmful. Higher-intensity CRRT does not improve clinical outcomes, and both fluid overload and excessive fluid removal should be avoided. However, the optimal CRRT protocol for patients with sepsis and its benefits remain uncertain. Although multiple RCTs have been conducted, their divergent findings can be attributed to heterogeneity in patient populations, differences in sepsis severity, and variations in AKI definitions. CRRT management must

TABLE 2. Key clinical studies evaluating CRRT intensity.

Authors (Year)	Study Design Intervention *vs.* Control	Main Findings
Palevsky *et al.* [54] (2008) ATN study	RCT Multicenter (27 VA/university-affiliated medical centers in the US) Patients: critically ill patients with AKI (SA-AKI: 63%) Intensive (n = 563) *vs.* Less-Intensive (n = 561) Intensive: 35 mL/kg/h CRRT or 6 times/week IHD/SLED Less-Intensive: 20 mL/kg/h CRRT or 3 times/week IHD/SLED Primary outcome: 60-day mortality	No significant difference was observed in 60-day mortality (Intensive 43.9% *vs.* Less-Intensive 43.7%). No significant differences were observed in the duration of RRT, recovery of kidney function, or non-renal organ failure.
Bellomo *et al.* [55] (2009) RENAL study	RCT Multicenter (35 ICUs in Australia and New Zealand) Patients: critically ill patients with AKI (SA-AKI: 49.4%) Higher (n = 747) *vs.* Lower (n = 761) Higher: 40 mL/kg/h CRRT Lower: 25 mL/kg/h CRRT Primary outcome: 90-day mortality	Higher-intensity CRRT did not reduce 90-day mortality (44.7% in both group). Hypophosphatemia was observed more frequently in the higher-intensity group than in the lower-intensity group.
Joannes-Boyau *et al.* [56] (2013) IVOIRE trial	RCT Multicenter (18 ICUs in France, Belgium, and the Netherlands) Patients: critically ill patients with septic shock and AKI HVHF (n = 66) *vs.* SVHF (n = 71) HVHF: 70 mL/kg/h CRRT SVHF: 35 mL/kg/h CRRT Primary outcome: 28-day mortality	28-day mortality was lower than expected but not different (HVHF 37.9% *vs.* SVHF 40.8%). No significant differences were observed in secondary endpoints, including 60- and 90-day mortality, duration of mechanical ventilation, duration of RRT, renal recovery, or ICU and hospital length of stay. HVHF was associated with a higher incidence of electrolyte disturbances, specifically hypokalemia and hypophosphatemia.
Fujii *et al.* [57] (2012)	Retrospective observational Study Two ICUs in Japan Patients: ICU patients treated with CRRT for AKI (SA-AKI: 55%) Lower-dose (n = 69) *vs.* Higher-dose (n = 62) Lower-dose: ≤16.7 mL/kg/h CRRT Higher-dose: >16.7 mL/kg/h CRRT Primary outcome: Hospital mortality	Low-dose CRRT did not increase mortality (Lower-dose 36% *vs.* Higher-dose 53%). No significant differences were observed in ICU mortality, 28-day ICU free days, and dialysis dependence among survivors.

RCT: Randomized Controlled Trial; AKI: Acute Kidney Injury; SA-AKI: Sepsis-Associated Acute Kidney Injury; CRRT: Continuous Renal Replacement Therapy; IHD: Intermittent Hemodialysis; SLED: Sustained Low-Efficiency Dialysis; RRT: Renal Replacement Therapy; ICU: Intensive Care Unit; HVHF: High-Volume Hemofiltration; SVHF: Standard-Volume Hemofiltration; ATN: Acute Renal Failure Trial Network; RENAL: Randomized Evaluation of Normal versus Augmented Level; IVOIRE: hIgh VOlume in Intensive care.

be dynamic and adapt to the constantly changing clinical status of the individual patient. In addition, most RCTs were powered for short-term mortality or renal outcomes rather than neurological outcomes, potentially limiting the ability to detect differential effects of CRRT on the brain. In previous studies, long-term outcomes were not assessed; these studies were primarily limited to short-term mortality and renal recovery. This leaves knowledge gaps regarding how CRRT influences long-term renal and neurological function in septic patients. Even after surviving sepsis, many patients experience long-term complications, including persistent cognitive impairment and chronic kidney disease. Accordingly, the assessment of long-term renal and neurological outcomes is crucial to understand the impact of CRRT in septic patients. In addition to a more detailed understanding of the pathophysiology of sepsis-induced brain and kidney injury in the presence and absence of CRRT, well-designed RCTs with standardized criteria and comprehensive evaluation of short- and long-term renal and

TABLE 3. Key clinical studies evaluating fluid management.

Authors (Year)	Study Design	Main Findings
Vincent JL *et al.* [37] (2006) SOAP study	Prospective observational cohort study Multicenter (198 ICUs from 24 European countries) Patients: ICU patients (n = 3147) Objective: To better define the incidence of sepsis and the characteristics of critically ill patients in European intensive care units	Sepsis was present in 37% of patients and was associated with ICU mortality. A positive fluid balance was one of the strongest prognostic factors for death.
Vaara *et al.* [38] (2012) FINNAKI study	Prospective observational cohort study Multicenter (17 ICUs in Finland) Patients: RRT-treated critically ill patients (n = 296) Objective: To study the association between fluid accumulation at RRT initiation and 90-day mortality	Patients with fluid overload at RRT initiation had twice the crude 90-day mortality compared to those without. Fluid overload was associated with increased 90-day mortality even after adjusting for disease severity, timing of RRT initiation, RRT modality, and the presence of severe sepsis. Severe sepsis was present in 48% of patients.
Bellomo *et al.* [39] (2012) RENAL study *post-hoc*	*Post-hoc* analysis of RCT (RENAL trial cohort) Cohort of 1453 patients enrolled in the RENAL study Objective: To examine associations between mean daily fluid balance during ICU and clinical outcomes	Negative mean daily fluid balance was consistently associated with improved clinical outcomes, including 90-day mortality, RRT-free days, ICU-free days, and hospital-free days.
Murugan *et al.* [40] (2019) RENAL study *post-hoc*	*Post-hoc* analysis of RCT (RENAL trial cohort) Cohort of 1434 patients enrolled in the RENAL study Objective: To examine the association of NUF with survival among critically ill patients with AKI Three groups were defined: Low: NUF rate $<$1.01 mL/kg/h Middle: NUF rate 1.01–1.75 mL/kg/h High: NUF rate $>$1.75 mL/kg/h	NUF rates greater than 1.75 mL/kg/h were associated with lower survival compared with NUF rates less than 1.01 mL/kg/h. Every 0.5 mL/kg/h increase in NUF rate was associated with increased mortality. Hypophosphatemia was observed more frequently in the high-tertile group compared with the middle- and low-tertile groups.

ICU: Intensive Care Unit; RRT: Renal Replacement Therapy; RCT: Randomized Controlled Trial; NUF: Net ultrafiltration; AKI: Acute Kidney Injury; SOAP: Sepsis Occurrence in Acutely ill Patients; FINNAKI: Finnish Acute Kidney Injury; RENAL: Randomized Evaluation of Normal versus Augmented Level.

neurological outcomes are needed.

In addition to optimizing the CRRT protocol, it is also necessary to explore other potential interventions to protect the kidneys. One recently discussed approach is intravenous amino acid infusion [60]. Under conditions of renal hypoperfusion, amino acid infusion may enhance renal functional reserve. Jufar *et al.* [61] reported that, in animal studies, amino acid infusion increased renal perfusion, renal oxygenation, and glomerular filtration rate. Furthermore, in the Intravenous Amino Acid Therapy for Kidney Protection in Cardiac Surgery (PROTECTION) trial, amino acid infusion reduced the incidence of postoperative AKI in adult patients undergoing cardiac surgery with cardiopulmonary bypass [62].

This review has several limitations. PubMed and MEDLINE searches were used to identify relevant studies, however, they may be subject to selection bias, and formal assessment of study quality was not conducted. Despite these limitations, this review aims to integrate both clinical and preclinical evidence to assess the influence of CRRT protocol on renal and neurological outcomes. Overall, this review identifies key knowledge gaps and proposes future research directions.

6. Conclusions

SA-AKI remains a major challenge in critical care. CRRT is essential for hemodynamically unstable patients; however, its impact on survival, renal recovery, and neurological outcomes remains uncertain. While CRRT provides vital renal support, its effects on cerebral tissue perfusion and oxygenation, neuroinflammation, and renal microcirculation are poorly understood. The interplay between CRRT, systemic and renal hemodynamics, cerebral autoregulation, and inflammation in sepsis warrants detailed mechanistic investigation to identify strategies that minimize secondary injury to both the brain and kidneys. Such mechanistic insights are critical for providing a strong scientific rationale for designing optimized CRRT protocols and translational studies. Optimizing CRRT in SA-AKI holds the potential to not only enhance renal recovery but also to provide broader organ protection, particularly for the brain, thereby improving overall patient prognosis.

ABBREVIATIONS

AKI, acute kidney injury; SA-AKI, sepsis-associated acute kidney injury; ICU, intensive care unit; CKD, chronic kidney disease; CRRT, continuous renal replacement therapy; RCT, randomized controlled trial; BBB, blood–brain barrier; KDIGO, Kidney Disease: Improving Global Outcomes; ELAIN, Early *vs*. Late Initiation of Renal Replacement Therapy in Critically Ill Patients with Acute Kidney Injury; AKIKI, Artificial Kidney Initiation in Kidney Injury; STARRT-AKI, Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury; IDEAL-ICU, Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit; SOFA, Sequential Organ Failure Assessment; VA/NIH, Veterans Administration/National Institutes of Health; ATN, Acute Renal Failure Trial Network; RENAL, Randomized Evaluation of Normal versus Augmented Level; IVOIRE, hIgh VOlume in Intensive care; LIMIT, Low-Intensity versus Medium-Intensity Continuous Kidney Replacement Therapy; HVHF, High-Volume Hemofiltration; SVHF, Standard-Volume Hemofiltration; SOAP, Sepsis Occurrence in Acutely ill Patients; FINNAKI, Finnish Acute Kidney Injury; BUN, blood urea nitrogen; RIFLE, Risk, Injury, Failure, Loss, End-stage kidney disease.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

MK and YL—conceived, designed, curated, and wrote the manuscript. TaF, CM, ES, ToF and YL—provided critical intellectual input into the scope, synthesis, and narrative of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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